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Original Article

Sodium oxybate treatment in narcolepsy and its effect on muscle tone

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ABSTRACT

Aims: To estimate the effect of the compound sodium oxybate (SO) on chin muscle tone in sleep, a re-analysis of the results of the international multicenter study SXB-15 was performed, applying a validated semi-automatic analysis of muscle tone. This analysis distinguishes short (<0.5 s) and long (>0.5 s) muscle activity indices per hour (SMI, LMI) in 116 patients with narcolepsy-cataplexy. While stable stimulant medication was permitted, tricyclics and SSRIs were withdrawn. Polysomnographies were performed at baseline (V5), four weeks after titration of SO to 4.5 g, 6 g, or 9 g or placebo (V6) and after another four weeks on stable SO dose (V7).

Results: SMI and LMI decreased significantly during light sleep. LMI remained stable in all SO groups during slow wave sleep (SWS), but decreased significantly during REM sleep. SMI decreased non-significantly, but consistently during SWS and REM in the 9 g group only. A subgroup analysis of patients who stayed on stimulants showed that they had higher SMIs and LMIs in all groups. Patients who had been treated with anticataplectic medication prior to study inclusion had lower LMIs in the 9 g group during REM sleep in all visits.

Conclusion: SO has a differential effect on muscle tone that is dose and sleep stage dependent. Low dosages increase short muscle activity, possibly enabling the occurrence of parasomnias. High doses are especially efficacious in REM sleep, suggesting that SO could be used to treat REM sleep behavior disorder. Comedication with stimulants and prior medication with anticataplectic medication exerts an influence on muscle tone.

1. Introduction

There are only a few studies that examine muscle tone throughout sleep stages [1–6]. The analysis of muscle tone has gained importance when evaluating polysomnographies for parasomnias, especially for REM sleep behavior disorder. Methods to evaluate muscle activity in sleep by visual analysis have been cumbersome and time consuming [7]. New automatic methods have been developed in the recent years [8–10]. Few of them have been validated [10–12]. Most of the studies have been used to analyze REM sleep without atonia (RWA) for REM sleep behavior disorder. To the best of our knowledge no study has ever systematically tried to analyze the effect of medication on muscle tone in narcolepsy patients.

In 2003 the FDA released the drug sodium oxybate (SO) for the treatment of narcolepsy-cataplexy. The authors observed that treatment with SO improved RBD in some patients with narcolepsy. RBD is a frequent co-morbid disorder of narcolepsy [13] and RWA is frequently registered in narcolepsy patients without clinically manifest RBD [5]. The authors therefore asked the drug company Jazz Pharmaceuticals (Palo Alto, USA) for permission to use the polysomnographies (PSGs) of the phase three sodium oxybate study SXB-15 [14] with the aim to re-analyze the data for muscle tone. The study protocol of this eight-week, randomized, double-blind, placebo-controlled parallel-group multicenter study is presented in Fig. 1. The study protocol was approved by the ethics committees of all participating centers.

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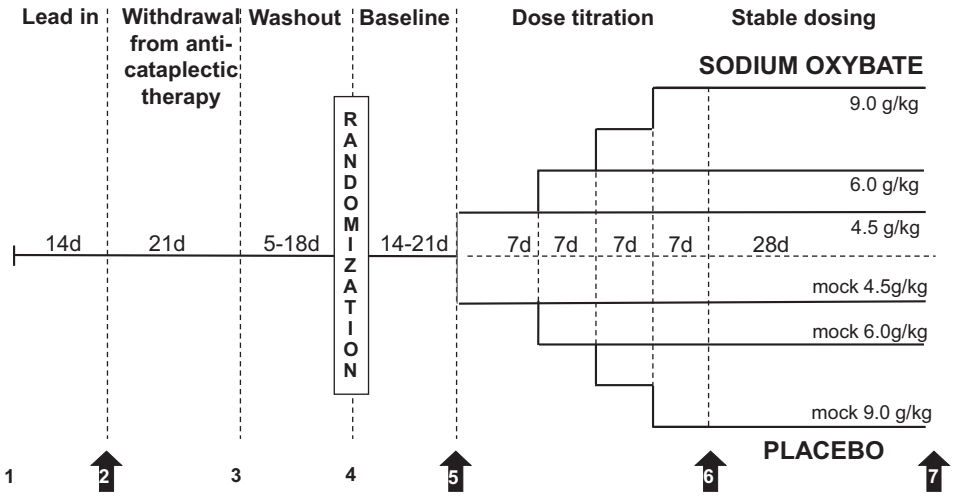

Fig. 1. Sodium Oxybate: Eight-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Multicenter Study. Bold arrows indicate visits (V1–V7) with polysomnographies and MWTs.

2. Methods

The SXB-15 study data comprised the codes of the participating centers, the patient's randomization to placebo (group 1), 4.5 g SO (group 2), 6 g SO (group 3), 9 g SO (group 4), completed visits, comedication and co-morbidity. None of the patients had co-morbid clinically manifest RBD which was an exclusion criterion. Several patients had to be excluded due to missing data. A dataset of 171 patients who finished the study was provided to the authors from 37 out of 42 participating centers. Several patients had to be excluded due to missing data. In four cases, only one single PSG has been retrieved and in 11 patients visit 5 (V5) was missing. Of the156 remaining patients either visit 6 (V6, n = 22) or visit 7 (V7, n = 11) were not provided. Since the causes for the missing visits could not be found in the database, the authors decided to exclude them. Another five patients were excluded by the authors due to presence of severe RLS and another two due to intake of buproprion and naloxone. Finally 116 patients were available for analysis with the complete dataset for V5, V6 and V7.

Artefact removal and sleep stage scoring was performed by two experienced scorers. The analysis of the muscle activity was performed according to Mayer et al. 2008 [6]. This semi-automatic analysis classifies motor events per hour, representing short (<0.5 s) and long (>0.5 s) muscle activity indices (SMI and LMI) similar to the analysis of periodic leg movements in sleep.

The results were separately analyzed for the complete PSG recording time (total), light sleep (stages N1 and N2), slow wave sleep (stage N3) and REM sleep. Most of the patients remained on stimulants (n: 93 vs. 33). For the subgroup analysis (patients with and without stimulants) we had to exclude another 11 patients according to the study protocol, because stimulants had been tapered only one week prior to study onset or after V5. The anti-cataplectic medication was washed out 5–18 days prior to run in phase in a group of 44 patients. We performed separate statistics for patients with and without stimulants and patients with and without previous anticataplectic medication to rule out medication effects on muscle tone [15].

3. Statistics

All statistics were performed with Statistica 12.7. MANOVAs were performed for all sleep stages, medication groups followed by LSD (least square distribution) tests, if available. Additional MANOVAs included the (previous) intake of anticataplectics and stimulants. Since MANOVS do not provide significant results if the direction of changes does not differ in time (visits) and groups (SO dosages), t-tests for paired samples were performed, followed by alpha adjustments for multiple comparisons by Cross & Chaffin [16], resulting in overall P-values for SMI and LMI changes to baseline (32 comparisons each). T-tests were also performed to assess dose dependent sleep stage duration changes. All groups showed normal distribution.

4. Results

4.1. Demographics

Table 1
Demographics.

Dose	N	Age, mean ± SD	Sex	Patients with stimulants	Pat. with previous anticataplectics
Placebo	27	41.67 ± 17.49	9 m, 18 f	19	13
4.5 g	34	41.35 ± 17.03	13 m, 21 f	26	15
6.0 g	33	39.39 ± 17.11	11 m, 22 f	22	9
9.0 g	22	38.27 ± 11.85	10 m, 12 f	18	11

4.2. Sleep stages

REM duration decreased significantly in a dose dependent way ($p < 0.0005$) and over time ($p < 0.0005$) resulting in a significant interaction between group and time for REM sleep duration ($p < 0.003$). In contrast, slow wave sleep (sleep stage N3) increased dose-dependently over time ($p < 0.001$), in particular in the 9 g group (see suppl. material). There was no change in light sleep (sleep stages N1 and N2) duration throughout all visits and groups.

4.3. Duration of movements

The duration of short muscle activity decreased over time ($p = 0.001$). Compared to baseline this decrease was significant after intake of 4.5 g over four (V6) and eight weeks (V7) ($p < 0.01$ each). In the 6.0 g group we found a trend at V6 ($p < 0.1$) and a significant reduction at V7 ($p < 0.05$). There was no effect in the 9 g group. Beside a general decrease of the duration of long muscle activity